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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/462,962	06/25/2001	STEPHEN PHILIP JACKSON	MEWE-010	5713

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EXAMINER	
ROBINSON, HOPE A	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 09/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/462,962	JACKSON ET AL.	
	Examiner	Art Unit	
	Hope A. Robinson	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31 and 34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 January 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1656.

2. Applicant's response to the Office Action mailed January 11, 2005 on July 18, 2005, is acknowledged.

Claim Disposition

3. Claims 1-30, 32-33 and 35 have been canceled. Claims 31 and 34 are pending and under examination.

Maintained-Claim Objection

4. Claim 31 remains objected to because of the following informalities:

For clarity and precision of claim language it is suggested that the claim is amended to recite:

> An assay method for identifying a compound able to modulate the interaction between (A) ATM (Ataxia-telangiectasia mutated) or ATR (ATM-Rad3-related) and (B) p53, the method including the steps of:
>
> (a) bringing into contact (i)ATM or ATR or a fragment of ATM or ATR which phosphorylates p53, (ii) p53 or a fragment of p53 which includes a site which is phosphorylated by ATM or ATR and (iii) a test compound; and

(b) determining phosphorylation at said site,

wherein an increase or decrease in the phosphorylation at said site in the presence relative to the absence of the test compound being indicative that the compound is able to modulate the interaction between ATM or ATR and p53.

Note that the numbering pattern in the claim is inconsistent.

Correction is required.

Maintained-Claim Rejections - 35 USC ∋ 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103 (a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103 (c) and potential 35 U.S.C. 102 (f) or (g) prior art under 35 U.S.C. 103 (a).

6. Claims 31 and 34 remain rejected under 35 U.S.C. 103 (a) as being unpatentable over Hoekstra et al. (WO 97/18323, May 22, 1997) in view of Meyn (Cancer Research , vol. 55, pages 5991-6001, 1995).

Hoekstra et al. teach an assay for identifying modulators of an ATM (identified as the cell cycle checkpoint phosphatidylinositol kinase related protein) and MCSS1 interaction, which is similar to p53, that involves contact with a test compound and a determination/quantification step (claim 31; see abstract, page 11 and claim 26 of the reference). Hoekstra et al. state that if a particular form of cancer results from a mutation in a gene, such as p53, an agent that inhibits the transcription or the enzymatic activity may be used to render cancerous cells more sensitive to chemotherapy or radiation therapy (page 11). In-so-far-as Hoekstra et al. does not explicitly teach the modulation of the interaction between ATM and p53, Meyn teach that ATM physically interacts with p53 (page 5998) and suggests that ATM can phosphorylate p53 (claim 31). It is well known in the art that ATM is part of a pathway that responds to DNA damage from ionizing radiation, thus ATM selectively regulates distinct p53-dependent cell cycle checkpoint and apoptotic pathways, a compound that modulates ATM will affect the interaction of ATM with p53 and modulate phosphorylation of p53 by ATM (claim 34).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Hoekstra et al. and include that modulation of ATM affects the interaction between ATM and p53 because Meyn state that ATM is upstream of p53 and that ATM and p53 physically interact (page 5998), thus inhibiting ATM would therefore affect the interaction between p53 and ATM. In addition, Meyn suggests that ATM,

which acts similarly to DNA-PKcs, can phosphorylate p53 (page 5997). The skilled artisan would therefore, be motivated to add in the effect that modulating ATM affects the interaction of ATM with p53, because Hoekstra et al. disclose an assay method to identify compounds that modulate ATM and agents that would modulate genes such as p53, stating that the therapeutic value in such an agent lies in the fact that current radiation therapy or chemotherapy does nothing to overcome the ability of the p53 mutant cancerous cell to sense and correct the DNA damage imposed as a result of the treatment. Furthermore, it is known in the art that p53 induction is significantly reduced following exposure to ionizing radiation in AT cell lines, which demonstrates the need for said compound.

Thus, the claimed invention was obvious to make and use at the time it was made and was *prima facie* obvious.

7. Claims 31 and 34 remain rejected under 35 U.S.C. 103 (a) as being unpatentable over Hoekstra et al. (WO 97/18323, May 22, 1997) in view of Baskaran et al. (Letters to Nature, vol. 387, pages 516-519, 1997).

Hoekstra et al. teach an assay for identifying modulators of an ATM (identified as the cell cycle checkpoint phosphatidylinositol kinase related protein) and MCSS1 interaction, which is similar to p53, that involves contact with a test compound and a determination/quantification step (claim 31; see abstract, page 11 and claim 26 of the reference). Hoekstra et al. state that if a particular form of cancer results from a mutation in a gene, such as p53, an agent that inhibits the transcription or the enzymatic activity may be used to render cancerous cells more sensitive to chemotherapy or radiation therapy (page 11). In-so-far-as Hoekstra et al. does not explicitly

teach the modulation of the interaction between ATM and p53, Baskaran et al. teach that ATM phosphorylates c-Abl and other proteins and that c-Abl and p53 are downstream targets of ATM, thus suggests that ATM can phosphorylate p53 (claim 31, see page 517 of the reference). As it is well known in the art that ATM is part of a pathway that responds to DNA damage from ionizing radiation, thus ATM selectively regulates distinct p53-dependent cell cycle checkpoint and apoptotic pathways, a compound that modulates ATM will affect the interaction of ATM with p53 and modulate phosphorylation of p53 by ATM (claim 34).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Hoekstra et al. and include that modulation of ATM affects the interaction between ATM and p53 because Baskaran et al. state that ATM is upstream of p53 and that ATM and p53 interact (page 517), thus inhibiting ATM would therefore affect the interaction between p53 and ATM. In addition, Baskaran et al. suggests that ATM phosphorylates p53 as it phosphorylates c-Abl and other proteins. The skilled artisan would therefore, be motivated to add in the effect that modulating ATM affects the interaction of ATM with p53, because Hoekstra et al. disclose an assay method to identify compounds that modulate ATM and agents that would modulate genes such as p53, stating that the therapeutic value in such an agent lies in the fact that current radiation therapy or chemotherapy does nothing to overcome the ability of the p53 mutant cancerous cell to sense and correct the DNA damage imposed as a result of the treatment. Furthermore, it is known in the art that p53 induction is significantly reduced following exposure to ionizing radiation in AT cell lines, which demonstrates the need for said compound.

Thus, the claimed invention was obvious to make and use at the time it was made and was *prima facie* obvious.

Response to Arguments

8. The response filed on July 18, 2005 has been considered. The objections and rejections of record have been maintained for the reasons set forth above and herein. Regarding the rejection under 35 U.S.C. 103 (a), on page 3+ applicant states that the examiner misinterpreted the references (see page 3 of response) and that Hoekstra is silent on the phosphorylation of p53 by ATM which applicant opines is not remedied by Meyn. It is further stated on page 4 that Meyn offers two possibilities, which are listed on page 4 of the response and discussed on page 5998 (left column) of the reference. Applicant argues that "Meyn provides only a speculative hypothesis that p53 might be involved in the induction of DNA damage induced apoptosis and suggest that if this hypothesis is true, then p53 might physically interact with ATM in some unspecified way, or it might not".. It is further stated that "this is neither experimental evidence nor positive teaching in Meyn that there is any physical interaction between p53 and ATM...". Applicant's arguments are not persuasive. The rejection is made under 35 U.S.C. 103(a) because all that is required is a mere suggestion, which applicant agrees is present in the reference by Meyn. Applicant states that Meyn does not provide experimental evidence or positive teaching, however, such is not required under 35 U.S.C. 103. If experimental evidence existed in the Meyn reference a rejection would have been instituted under 35 U.S.C. 102(b). The Meyn et al. reference suggests that ATM physically interacts with p53 in a way that inhibits p53-mediated apoptosis indirectly, thus the reference is relevant to the claimed invention.

Applicant on page 3 of the response state, that "Meyn does not teach that ATM physically interacts with p53 and does not suggest that ATM can phosphorylate p53. This argument is not persuasive. On page 5997 of the Meyn reference it is stated that DNA-PK activates its DNA-PKcs subunit, which can then phosphorylate a variety of proteins *in vitro* including p53 (right column). It is also stated that "the similarities between ATM and DNA-PKcs suggest that, like DNA-PKcs, the ATM protein may be directly involved in the recognition of DNA damage, perhaps serving as the protein kinase subunit of a functional complex that also includes ku70 and ku80-like polypeptides. It is also disclosed that the ATM protein has PI3 kinase domain. Meyn states that mammalian PI3-kinase and yeast PI3-kinase phosphorylates proteins reinforcing the possibility that the true targets of the phosphotransferase activity of the ATM protein may be proteins. Therefore, the Meyn reference establishing that there is a possibility that ATM has phosphorylation activity and the likeness made with DNA-PKcs suggests that ATM acts similarly (and the reference discloses that with DNA-PKcs phosphorylates p53). Therefore, the rejection remains as the reference remains relevant to the claimed invention.

On page 5 of the response applicant applies the same reasoning above to the 103(a) rejection of record over Hoekstra in view of Baskaran, indicating that the references do not teach the invention as claimed. Specifically on page 6 applicant states that Baskaran makes no suggestion that their experiments show that ATM acts directly on p53 and c-Abl rather than via intermediate members of different pathways. It is stated that c-Abl and p53 are distinct downstream targets of ATM which applicant interprets to mean different pathways and function. This argument is not persuasive. Applicant indicates that a showing of direct action on p53 is not

shown in the reference, however applicant is arguing a limitation not is not evidenced by the present claim language as there is no recitation of "ATM acts directly on p53", the claim simply recites "interaction". On page 516 of the Baskaran reference it is disclosed in the abstract that "[T]hese findings identify the c-Abl tyrosine kinase as a downstream target of phosphorylation and activation of the ATM kinase in the cellular response to ionizing radiation. In addition, page 518 of the reference discloses that ATM kinase phosphorylated the GST-Abl-HP fragment on serine and that taken together, these results indicate that ATM kinase phosphorylates c-Abl at Ser 465 to activate tyrosine kinase activity. Therefore, the combined teaching of the references provides a suggestion for the claimed invention, which is primer facie obvious.

Conclusion

9. No claims are presently allowable.

10. Applicant's amendment necessitated the new/modified ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-0957. The examiner can normally be reached on Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr, can be reached at (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

DAVID J. STEADMAN, PH.D.
PRIMARY EXAMINER

Hope Robinson, MS HR
9/16/05
Patent Examiner